

A tale of two tracers

The age of wisdom for dementia diagnosis?

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Diagnostic minimalism is common for many practitioners as they evaluate patients with early signs of dementia. No doubt it is the lack of effective disease-modifying treatments that has led many to forsake aggressive diagnostic assessment, or at least to defer it, expecting the disease phenotype eventually to declare itself. In this issue of *Neurology*®, Rabinovici and colleagues¹ report a comparative study of 2 PET tracers, Pittsburgh compound B (PiB) and fluorodeoxyglucose (FDG), applied to a common clinical problem: patients who develop in their 60s the early signs of impairment that could represent either of the most common forms of dementia, Alzheimer disease (AD) or frontotemporal lobar degeneration (FTLD). The premise underlying this and related research is that early, precise dementia diagnosis is important. Patients, families, and doctors deserve the most accurate information about the disease-causing symptoms; prognostication, education, and planning, as well as symptomatic treatment, equally demand such information. Furthermore, disease-modifying treatment trials will likely be inefficient until we can identify the molecular pathology targeted by the treatment. The Rabinovici et al. report is timely because the diagnostic armamentarium for dementing disorders could soon be substantially augmented by the availability of a new form of molecular imaging, amyloid PET, which will perhaps soon be approved by the Food and Drug Administration. These developments prompt a careful evaluation of the relative diagnostic classification performance of FDG-PET and amyloid PET.

As the authors point out, the US Centers for Medicare and Medicaid Services approved reimbursement of FDG-PET nearly a decade ago for the differential diagnosis of AD vs FTLD, based largely on autopsy data relating AD pathology to FDG hypometabolism in temporoparietal association cortex (reviewed in 2). More recent autopsy studies have confirmed these findings,^{3,4} but have also shown the

value of FDG-PET in improving diagnostic confidence when expert clinicians sought to differentiate AD and FTLD.^{5,6}

In the present study, 107 patients with early-onset AD or FTLD, 12 with known histopathology, underwent both FDG-PET and amyloid PET with PiB. Images were classified as either AD- or FTLD-like by a pair of blinded qualitative, visual readers; also assessed were quantitative measures of tracer uptake and cutpoint thresholds of abnormality. FDG-PET was AD-like if tracer uptake was more abnormal in temporoparietal than in either frontal or temporal (FTLD-vulnerable regions) and was FTLD-like if metabolism was worse in the FTLD-vulnerable areas. PiB PET was classified as AD-like if it exceeded a threshold based on the mean of a PiB-negative normal control group, and as FTLD if it did not exceed this threshold.

PiB qualitative and quantitative assessments were virtually identical, consistent with the large difference in retained tracer after 90 minutes in most amyloid-positive patients, compared to most amyloid-negative patients. In contrast, quantitative FDG specificity was substantially greater than the qualitative visual interpretation, similar to a previous report.⁵

The samples were carefully chosen to be of roughly comparable clinical dementia severity (Mini-Mental State Examination and Clinical Dementia Rating sum of boxes). Using clinical diagnosis as the truth standard, PiB was more sensitive than FDG for the identification of patients with a clinical diagnosis of AD. Specificities were similar based on visual reads, but with quantitative measurement FDG outperformed PiB. Autopsy data are a stronger basis for evaluating PET than clinical classifications, and here the edge for PiB is not as clear. One case with high PiB and AD histopathology also had FTLD-like hypometabolism, a well-known if unusual circumstance. This was the only case of the

See page 2034

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10 in which quantitative FDG data were available and incorrect.

These data are convincing that the presence or absence of AD neuropathology in these 2 dementias can be determined by the use of PiB, and that PiB—whether read visually or analyzed quantitatively—is also highly sensitive to the clinical diagnosis of AD. FDG, on the other hand, may still play an important role by improving the specificity of the diagnosis of AD (i.e., in this case to identify FTLT). The authors point out that the use of FDG in clinical settings is less consistent than PiB with regard to interrater reliability, especially when a quantitative comparison with a group of normal subjects is not available. One unstated conclusion is that such quantitative FDG comparisons could improve clinical practice and should be more widely adopted. A recent report focused on a different regional strategy for identifying FTLT-like FDG patterns, in which greater emphasis placed on anterior cingulate and anterior temporal regions resulted in greater accuracy.⁶ Thus, it is possible that the method used here underestimated the value of FDG in differential diagnosis of AD vs FTLT since a substantial proportion of patients with FTLT exhibit temporoparietal hypometabolism.

The authors are appropriately cautious about generalizing these conclusions to situations in which other confounding features, such as older age and vascular disease comorbidity, are present. They point out that PiB will likely have less value in differentiating AD from DLB since many patients with DLB have relatively high uptake consistent with amyloid pathology⁷ and in differentiating among amyloid-negative dementias.

Further research will be necessary to determine the best place for amyloid PET in relation to FDG-PET, MRI, spinal fluid analysis, and other tests in the recommended sequence of diagnostic evaluations of patients with dementia, which will likely vary depending on the setting and the goals. As these new tests become more widely available, practically oriented investigations such as the present study will

contribute in important ways to the dialogue—necessary in our community—aiming to balance diagnostic rigor with cost effectiveness. We hope that these discussions will soon be taking place in an era in which we have effective disease-modifying therapies, which would truly be the best of times.

AUTHOR CONTRIBUTIONS

Dr. Johnson: drafting/revising the manuscript. Dr. Dickerson: drafting/revising the manuscript, analysis or interpretation of data.

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